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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,592	08/27/2003	Noubar B. Afeyan	COTH-P01-001	7920

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EXAMINER	
MEAH, MOHAMMAD Y	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,592	AFEYAN ET AL.	
	Examiner	Art Unit	
	Mohammad Meah	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *56,110,135,137,147 and 150* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 107, 108, 117, 127-129, 131-134, 150, 156 and 157* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 5,7-9,26,29,31,35,37,48-51,56,58,69,70,72,74,76,78,107,108,110,117,127-129,131-135,137,147,150,156 and 157.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 10/26/07 has been entered.

Claims 5, 7-9, 26, 26, 29, 31, 35, 37, 48-51, 56, 58, 69-70, 72, 74, 76, 78, 107, 108, 110, 117, 127-129, 131-135, 137, 147, 150, 156 and 157 are pending. Claims 56, 110, 135, 137, 147 and 150 remain withdrawn. Claims *5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 107, 108, 117, 127-129, 131-134, 150, 156 and 157* will be examined.

Claim Rejections

35 U.S.C 112

35 USC 112 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5 and 7-9, 26, 26, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 107, 108, 117, 127-129, 131-134, 150, 156 and 157 (dependent on claim 5) are rejected

under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention.

Claims 5 – the recitation of the term "bimolecular accretion" makes the claim indefinite. What is "bimolecular accretion" ? Paragraph 224 of the specification define some extend the term bimolecular accretion, but the bimolecular accretion as defined is too board and indefinite.

Rejection of claim 5 under USC 112 *2nd paragraph* requirement is withdrawn after amendment of the claim by the examiner.

35 U.S.C 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 107, 108, 117, 127-129, 131-134, 150, 156 and 157 (dependent on claim 5) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of

the claimed invention. Claim 5 is directed to an adzyme comprising any protease conjugated optionally through a linker polypeptide with any a targeting polypeptide wherein said target polypeptide reversibly binds any substrate comprising bimolecular accretion and wherein said protease cleave any peptide bond within said bimolecular accretion moiety. The specification teaches the structure of only a few such fusion proteins or "adzymes" and said substrate.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the

variation within the genus.

A bimolecular accretion as defined in paragraph 224 of the specification may be an constituent moiety comprising "any undesirable assemblage of biomolecules, usually one that brings together components that are not typically found in an assemblage together usually one that has grown over time by the successive addition of material. Accretions are generally large enough as to be non-diffusible (although clots are accretions that may diffuse in the circulatory system) and are generally larger than the size of a typical host cell. Bimolecular accretions will often contain dead and living cells as well as extracellular matrix. Examples of bimolecular accretions include amyloid deposits, e.g., a .beta.-amyloid peptide deposit characteristic of Alzheimer's disease or a type II diabetes amyloid deposit, a collagen deposit, a protein deposit, an atherosclerotic plaque, an undesirable fat mass, an undesirable bone mass, a blood clot, or a cyst."

It is unclear how fusion protein comprising protease approach to and then can catalyze the cleavage of such diverse bimolecular accretion moiety. The specification lacks description of any additional species and identifying characteristics or properties or structure correlated with function. Therefore one of skill in the art would not recognize from the disclosure that applicants' were in possession of the claimed invention.

Applicants' are referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 107, 108, 117, 127-129, 131-134, 150, 156 and 157 (dependent on claim 5) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an adzyme or bifunctional fusion protein wherein prethrombin is conjugated via a linker with scFvαHA (antibody) or trypsin is conjugated via a linker with sp55 of TNFR1 or anti-TNFα scFV antibody and wherein conjugated prethrombin can cleave a peptide bond on plasmogen, does not reasonably provide enablement for any adzyme comprising any protease conjugated optionally through a linker polypeptide with any targeting polypeptide wherein said target polypeptide reversibly bind any bimolecular accretion moiety and wherein said protease cleave any peptide bond within said bimolecular accretion moiety. It is well known to person knowledgeable in prior art that active protein usually does not react with precipitated and inactive protein. Bimolecular accretion moiety comprising dead cell, and other precipitated proteins may not be accessible to active protease and therefore may not be cleaved by said protease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of

the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claim(s).

Claims 5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 107, 108, 117, 127-129, 131-134, 150, 156 and 157 are so broad as to encompass any adzyme comprising any protease conjugated optionally through a linker polypeptide with any a targeting polypeptide wherein said target polypeptide reversibly bind any bimolecular accretion and wherein said protease cleave any peptide bond of within said bimolecular accretion moiety . The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number adzymes made via conjugation of broad class of protease conjugated through a linker polypeptide with broad class of polypeptides targeting moieties and wherein target polypeptide reversibly bind any bimolecular accretion and wherein said protease cleave any peptide bond within said bimolecular accretion moiety . These claims are drawn to fusion proteins having virtually any structure wherein said fusion protein reversibly bind any bimolecular accretion moiety and subsequently cleave a peptide bond of said accretion moiety. Bimolecular accretion moiety comprising dead cell, and other precipitated protein may not be accessible to active protease and therefore may not be cleaved by said protease. In view of the great breaths of claims, amount of experimentation required to isolate specific protease and targeting domain molecule for fusion to make specific adzyme and , the lack of guidance, working examples, unpredictability of the art in predicting the function (adzyme activity) from protein's structure (Whisstock, et al. Quarterly Rev. Biophy. 2003, 36, pp

307-340), the claimed invention would require undue experimentation. As such the specification fails to teach one of ordinary skill how to use the full scope of the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only few fusion proteins of specific amino acid sequences.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any fusion protein of any antibody molecule or fragments or modified fragments thereof with any serine protease protein because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting adzyme activity; (B) the general tolerance of enzyme activity to modification and extent

of such tolerance; (C) a rational and predictable scheme for modifying any residues for adzyme activity with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly include fusion protein of any compound (antibody, peptide, protein or chemical targeting moiety) conjugated with any enzyme or any protein having enzyme activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of adzyme activity, having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicant's arguments, on pages 8-9 of their amendment against rejection of claims 131-132 under 35 U.S.C 112, first paragraph enablement requirement are acknowledged and found persuasive and therefore rejection of claims 131-132 is withdrawn.

CLAIM Rejection - 35 U.S.C 102

Rejection of Claims 5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 107, 108, 117, 127-129, 131-134, 150, 156 and 157 rejected under 35 U.S.C. 102(e) as being anticipated by Chen et al. (US 2003/0068792) is withdrawn. Applicants argument against Chen et al. (US 2003/0068792), is found persuasive mainly because; although Chan does teach fusion protein, however does not teach specific fusion protein wherein catalytic domain and targeting domain are discrete and heterologous with respect to each other. Therefore rejection based on Chen et al is withdrawn.

The 102 rejections of claims 5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 107, 108, 117, 127-129, 131-134, 150, 156 and 157 under 35 U.S.C. 102 using Holvoet et al. (JBC1991, vol.266, pp 19717-19724) of the previous office action are withdrawn after finding Applicants argument persuasive.

The 102 rejections of claims 5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 107, 108, 117, 127-129, 131-134, 150, 156 and 157 under 35 U.S.C. 102 Davis et al. (WO 00/64485) of the previous office action are withdrawn after amendment of claims. Specially Davis et al. (WO 00/64485) do not teach cleaving a peptide bond of substrate wherein said substrate is biological accretion moiety.

CLAIM Rejection - 35 U.S.C 103a

Claims 5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 107, 108, 117, 127-129, 131-134, 150, 156 and 157 are rejected under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) , Guo et al. (Biotec and Bioeng 2000, 70, 456-463) in view of Sallberg et al. (US 6960569) or whitcomb et al. (US PAT 6406846) is withdrawn after amendment of the claims. Davis et al. (WO 00/64485) do not teach cleaving a peptide bond of substrate wherein said substrate is **biological accretion moiety**.

Double Patenting Rejection

Provisional rejection of claims 5 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 35, 2 and 19 of copending is remain, since both specification teach adzyme wherein protease catalytic domain cleaves peptide bond of a substrate wherein said substrate is a **biological accretion**. Examiner agrees with applicant that provisional Double patenting rejection will be withdrawable upon allowance when applicant submit terminal disclaim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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